PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
VS:CE:FP18630		
International Application No.	International Filing Date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU2003/001373	16 October 2003	16 October 2002

International Patent Classification (IPC) or national classification and IPC

Int. Cl. [7] A61K 38/08, 38/12, A61P 19/02

Applicant

THE UNIVERSITY OF QUEENSLAND et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheet(s).

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of the report
14 May 2004	24 August 2004
Name and mailing address of the IPEA/AU	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	**G.R.PETERS** Telephone No. (02) 6283 2184

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/001373

I. Basis of the report

1. With regard to the elements of the international application:*

- [ ] the international application as originally filed.
- [X] the description, pages **1-32,** as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [X] the claims, pages , as originally filed,
  pages , as amended (together with any statement) under Article 19,
  pages , filed with the demand,
  pages **33-35,** received on **12 August 2004** with the letter of **11 August 2004**
- [X] the drawings, pages **1/6-6/6,** as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [ ] the sequence listing part of the description:
  pages , as originally filed
  pages , filed with the demand
  pages , received on with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

- [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- [ ] the language of publication of the international application (under Rule 48.3(b)).
- [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- [ ] contained in the international application in written form.
- [ ] filed together with the international application in computer readable form.
- [ ] furnished subsequently to this Authority in written form.
- [ ] furnished subsequently to this Authority in computer readable form.
- [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages
   - [ ] the claims, Nos.
   - [ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/001373

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**1-16**	**YES**
	Claims		**NO**
Inventive step (IS)	Claims	**1-16**	**YES**
	Claims		**NO**
Industrial applicability (IA)	Claims	**1-16**	**YES**
	Claims		**NO**

2. Citations and explanations (Rule 70.7)

The claims are now limited to the use of compounds of formula I and are thus considered to be novel and in compliance with article 33(2) of the PCT.

Claims 1- 16 also involve an inventive step as none of the citations disclose or suggest that G-protein coupled receptors as a class, have any utility in the treatment of osteoarthritis. Thus the claims comply with article 33(3) of the PCT.

The industrial applicability of the claims is not in doubt.

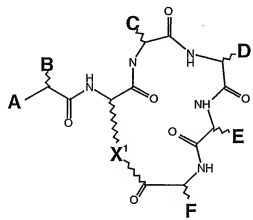
CLAIMS

1. A method of treatment of osteoarthritis, comprising the step of administering an effective amount of an inhibitor of a G protein-coupled receptor to a subject in need of such treatment, in which the inhibitor is a compound which

(a) is an antagonist of a G protein-coupled receptor,

(b) has substantially no agonist activity, and

(c) is a cyclic peptide or peptidomimetic compound of formula I



where A is H, alkyl, aryl, NH_2, NH-alkyl, $N(alkyl)_2$, NH-aryl, NH-acyl, NH-benzoyl, $NHSO_3$, $NHSO_2$-alkyl, $NHSO_2$-aryl, OH, O-alkyl, or O-aryl;

B is an alkyl, aryl, phenyl, benzyl, naphthyl or indole group, or the side chain of a D- or L-amino acid, but is not the side chain of glycine, D-phenylalanine, L-homophenylalanine, L-tryptophan, L-homotryptophan, L-tyrosine, or L-homotyrosine;

C is the side chain of a D-, L- or homo-amino acid, but is not the side chain of isoleucine, phenylalanine, or cyclohexylalanine;

D is the side chain of a neutral D-amino acid, but is not the side chain of glycine or D-alanine, a bulky planar side chain, or a bulky charged side chain;

E is a bulky substituent, but is not the side chain of D-tryptophan, L-N-methyltryptophan, L-homophenylalanine, L-2-naphthyl L-etrahydroisoquinoline, L-cyclohexylalanine, D-leucine, L-fluorenylalanine, or L-histidine;

F is the side chain of L-arginine, L-homoarginine, L-citrulline, or L-canavanine, or a bioisostere thereof; and

X is $-(CH_2)_nNH-$ or $(CH_2)_n-S-$, where n is an integer of from 1 to 4; $-(CH_2)_2O-$; $-(CH_2)_3O-$; $-(CH_2)_3-$; $-(CH_2)_4-$; $-CH_2COCHRNH-$; or $-CH_2-CHCOCHRNH-$, where R is the side chain of any common or uncommon amino acid.

2. A method according to claim 1, in which n is 2 or 3.

3. A method according to claim 1 or claim 2, in which A is an acetamide group, an aminomethyl group, or a substituted or unsubstituted sulphonamide group.

4. A method according to claim 3, in which A is a substituted sulphonamide, and the substituent is an alkyl chain of 1 to 6 carbon atoms, or a phenyl or toluyl group.

5. A method according to claim 4, in which the substituent is an alkyl chain of 1 to 4 carbon atoms.

6. A method according to any one of claims 1 to 5, in which B is the side chain of L-phenylalanine or L-phenylglycine.

7. A method according to any one of claims 1 to 6, in which C is the side chain of glycine, alanine, leucine, valine, proline, hydroxyproline, or thioproline.

8. A method according to any one of claims 1 to 7, in which D is the side chain of D-Leucine, D-homoleucine, D-cyclohexylalanine, D-homocyclohexylalanine, D-valine, D-norleucine, D-homo-norleucine, D-phenylalanine, D-tetrahydroisoquinoline, D-glutamine, D-glutamate, or D-tyrosine.

9. A method according to any one of claims 1 to 8, in which E is the side chain of an amino acid selected from the group consisting of L-phenylalanine, L-tryptophan

and L-homotryptophan, or is L-1-napthyl or L-3-benzothienyl alanine.

10. A method according to any one of claims 1 to 9, in which the inhibitor is a compound which has antagonist activity against C5aR, and has no C5a agonist activity.

11. A method according to any one of claims 1 to 10, in which the inhibitor has potent antagonist activity at sub-micromolar concentrations.

12. A method according to any one of claims 1 to 11, in which the compound has a receptor affinity IC50< 25μM, and an antagonist potency IC50< 1μM.

13. A method according to any one of claims 1 to 12, in which the compound is selected from the group consisting of compounds **1** to **6**, **10** to **15**, **17**, **19**, **20**, **22**, **25**, **26**, **28**, **30**, **31**, **33** to **37**, **39** to **45**, **47** to **50**, **52** to **58** and **60** to **70** described in PCT/AU02/01427.

14. A method according to claim 13, in which the compound is compound **1** (AcF-[OP-DCha-WR]), compound **33** (AcF-[OP-DPhe-WR]), compound **60** (AcF-[OP-DCha-FR]) or compound **45** (AcF-[OP-DCha-WCit]) described in PCT/AU02/01427.

15. A method according to any one of claims 1 to 14, in which the inhibitor is used in conjunction with one or more other agents for the treatment of osteoarthritis.

16. Use of a compound as defined in any one of claims 1 to 14 in the manufacture of a medicament for the treatment of osteoarthritis.